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A numerical study of rapid heating for high temperature radio frequency hyperthermia

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Abstract

Hyperthermia is a promising adjuvant cancer treatment modality. However, unresolved engineering problems with the production and regulation of temperature distributions within tissues in vivo have frustrated repeated efforts to implement clinical hyperthermia protocols. A major technical problem with hyperthermia production in vivo is the cooling effect caused by circulating blood in larger vessels. Larger blood vessels, when located in heated tumors, can prevent achievement of sufficiently high temperatures, resulting in loss of therapeutic effect. One possible way of circumventing this problem is the delivery of a critical heat dose during a short-term, high-temperature treatment episode to minimize cooling from blood flow. We investigated the concept of such rapid, high-temperature heating of tissue in a two-dimensional finite element numerical model. The model demonstrates the feasibility of interstitial radiofrequency delivery of a therapeutic heat dose, equivalent to 30 min at 43°C, to a 1 cm^3 tumor during a 60-s period. The model assumes circulation of cooling fluid through hollow electrodes. A post processor has been designed to display a 3-D image of the temperature distribution, electric field, and thermal dose delivered to a unit volume within the heated tissue.

Key words: Hyperthermia; Radio frequency heating; Finite element

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1. Introduction

Cancer remains a major disease with a yearly incidence of more than 1 000 000 new cases in the USA alone, leading to more than 500 000 deaths, according to American Cancer Society Facts and Figures, 1992. Neither cancer incident, nor cancer mortality is likely to decrease in the near future. Rapid progress in cancer research has increased the basic understanding of cancer biology, but has not translated into widely implemented successful treatment protocols. Therefore, continued improvement of conventional therapies is most likely to prolong productive lives, thus stemming the adverse economic impact of this disease.

Hyperthermia is a cancer treatment modality that can be highly effective when used as an adjuvant to chemotherapy, surgery, or radiation [1–3]. For example, the use of combined hyperthermia and X-radiation typically results in a doubling of local tumor control rates over optimal radiation therapy alone. However, the reproducible application of hyperthermia is technically difficult to achieve, especially with deep tumors [4,5]. Major technologies for generating hyperthermia in vivo include: (1) noninvasive microwave antennae (100–2450 MHz); (2) ultrasound applicators (focused, unfocused, transducer arrays); or (3) interstitial RF hyperthermia using electrodes that are implanted around the tumour periphery or thermoseeds that are implanted within the tumor. The minimum achieved tumor temperature has been shown to be a significant predictor variable for efficacy of a hyperthermia treatment [6]. In addition, Dewhirst [7] reported that the complete response rate and duration of response were related to the minimum achieved tumor temperature. At present, however, none of the commercially available hyperthermia equipment are capable of producing clinically desirable temperature distributions within a given volume of target tissue [3,5].

The lack of satisfactory heating devices can be traced to multiple causes, including tissue inhomogeneity and blood flow [6]. Theoretical evidence has long indicated that blood flow is a major factor in determining the minimum achieved tumor temperature [9–11]. It has been shown that tumor regrowth following hyperthermia often occurs near blood vessels, an indication that these cells may not have received an effective thermal dose [11,12]. Typical regional heat treatments are aimed at producing hyperthermia of approx. 30–45 min at temperatures in excess of 42°C, with the intent of remaining below the pain threshold of 45°C. A major difficulty in achieving this desired temperature range occurs due to the heat transfer properties of flowing blood. Intermediate-sized blood vessels provide sufficient cooling to prevent the required level of hyperthermia (i.e. 42°C) in tissue near the vessels. The idea of rapid high temperature hyperthermia is to heat target tissue to higher temperature in a shorter time to achieve the same hyperthermic effect as the traditional hyperthermia treatment. Consequently, the cooling effect of the blood flow can be minimized.

It has been known that the thermal damage cells experience due to heating is related to both the temperature of the cells and the time the cells are exposed to that temperature. This has led to the idea that thermal histories can be compared by introducing the concept of a heat 'dose' delivered to a target tissue. Although still untested in human tumors over a significant temperature range, in vitro and in vivo

data in mammalian cell models support the concept of a thermal dose [13,14]. According to Henle [13], a temperature history of 48°C for 55 s is equivalent to a thermal dose of 43°C for 30 min. This suggests that the heating time can be reduced from 30 min to 55 s if rapid heating is successful.

Several authors have described modeling of interstitial radiofrequency (rf) hyperthermia [9,15,16]. These papers describe a traditional hyperthermia protocol, where a tumor is heated to a uniform temperature and then held at that temperature for a preset time, often 30 min. Other authors [17–19] have proposed using scanned ultrasound to rapidly heat tissue to a high temperature in order to overcome the cooling effects of blood flow. We have developed a two-dimensional finite element numerical model to simulate a rapid, high temperature rf hyperthermia protocol. The simulations use a combined electrical-thermal model. The power deposition due to a 1 MHz voltage applied to a set of electrodes is calculated, as described by Strohbehn [15].

There are several advantages to the rapid radio frequency heating technique described above. First, it may be possible to stop blood flow to a tumor or an extremity containing a tumor for a period of one minute without harming healthy tissue downstream from the tumor. In such case, the variability in tumor temperature due to blood flow will be eliminated. After treatment, blood flow is allowed to return to normal. A two dimensional finite element program has been developed to simulate a rapid heating process by heating a set of electrodes implanted in the target tissue. The results show that a thermal dose equivalent to or greater than 30 min at 43°C can be achieved in 60 s for a 1 cm diameter tumor.

2. Method

A two-dimensional finite element numerical program HYFEM.FOR has been developed to simulate a rapid, high temperature hyperthermia protocol implemented by releasing power from electrodes implanted in a target tissue. It is written in FORTRAN and uses 9-node rectangular elements. The simulations use a combined electrical-thermal model. The thermal behavior of the tissue is described by the bioheat equation with no perfusion term:

$$\rho c \left(\frac{\partial T}{\partial t} \right) - \nabla \cdot (k \nabla T) = Q_s \tag{1}$$

where Q_s is a heating source term. For our case, the heating source comes from the electrical power of the electrodes. At the low frequencies of a few MHz, the electrical field can be found as the Strohbehn [15] gradient of a scalar potential that obeys Laplace's equation, similar to that in electrostatics:

$$-\nabla \cdot \sigma(T) \nabla V = 0 \tag{2}$$

where V is voltage and $\sigma(T)$ is the electrical conductivity. It is assumed that the electrodes are infinitely long, and small enough compared to the distance between them

so that they can be considered as a line sources. By assuming homogeneous electrical and thermal properties in the medium, the electrical potential from a single electrode can be calculated by

$$V_i = -\frac{\lambda_i}{2\pi\epsilon} \ln r_i \tag{3}$$

where V_i is the electrical potential from electrode i at a distance r_i and λ_i is line charge density. Then the electrical potential from N electrodes at any given point $r = (x,y)$ can be calculated from the formula:

$$V(r) = \sum_{i=1}^{N} V_i(r) = -\frac{1}{2\pi\epsilon} \sum_{i=1}^{N} \lambda_i \ln r_i \tag{4}$$

Because the electrical properties of tissue are mainly resistive at the frequencies used, magnetic fields can be ignored. Q_s, the local power density distribution can then be calculated as a derivation of the Poynting power theorem [20,21]

$$Q_s = \sigma(T)\left[\left(\frac{\partial V}{\partial x}\right)^2 + \left(\frac{\partial V}{\partial y}\right)^2\right] \tag{5}$$

Once Q_s is given, temperatures can be numerically calculated from Eq. 1 at each node for each time step. It is known that the thermal damage cells experience due

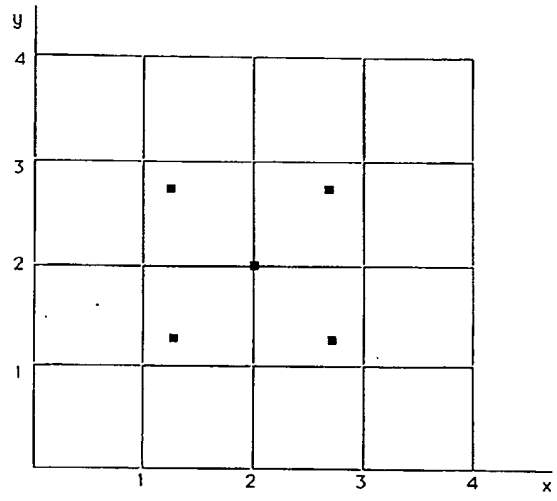

Fig. 1. Target tissue with five electrodes.

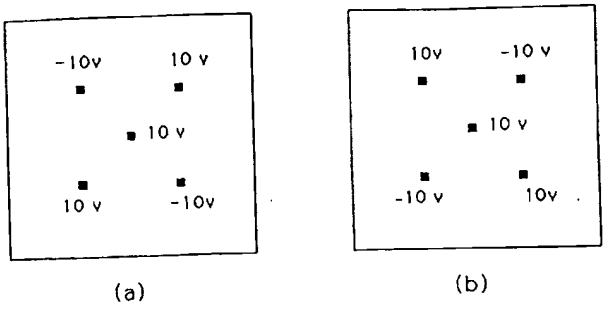

Fig. 2. Two different power patterns of the electrodes.

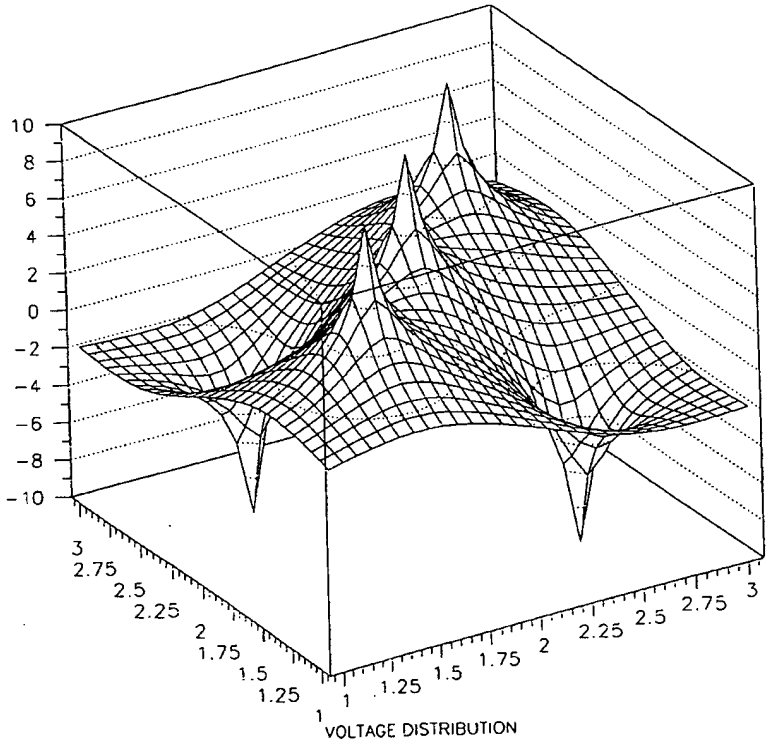

Fig. 3. Voltage distribution.

to heating is related to both the temperature of the cells and the time the cells are at that temperature [1,13]. This has led to the idea that thermal histories can be compared by introducing the concept of a heat 'dose' delivered to a target tissue. An empirical equation in Henle et al. [13] can be used to convert any specific time-temperature relationship into an equivalent biological dose for a given heating time and an arbitrary temperature. This equation can be stated as:

$$t_R = \int_{t_0}^{t_f} \exp b(f(t) - T_R)dt \tag{6}$$

where b is an empirical constant = 0.7 for temperatures above 43°C and = 0 for temperature below 43°C, $f(t)$ is an expression describing the actual time-temperature history that cells experience, T_R is a reference temperature, and t_R is the equivalent heating time at the reference temperature, T_R. Cells heated with a non-constant temperature $f(t)$ should exhibit the same biological effects as if they had been heated

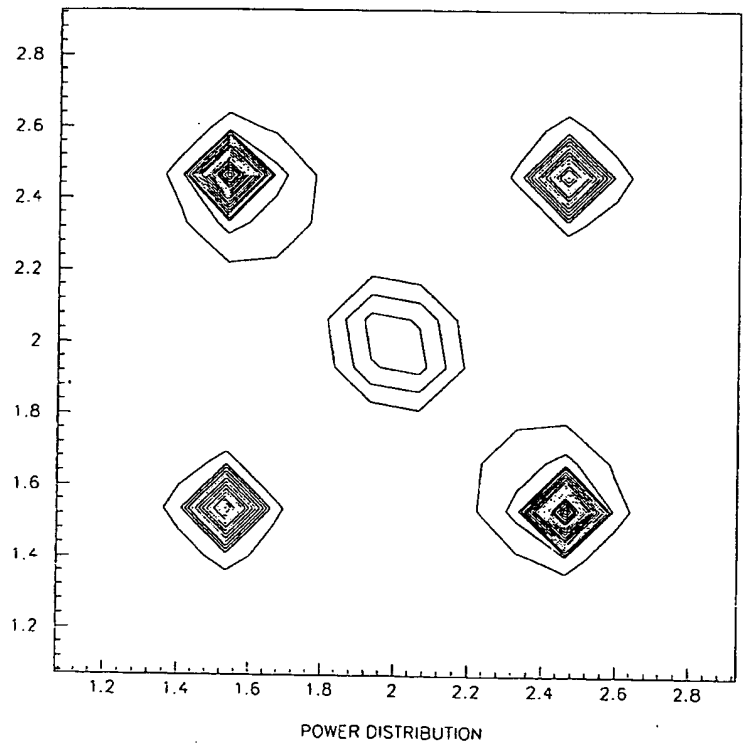

Fig. 4. Power distribution contour.

at T_R for a time of t_R. For example, according to Eq. 6 a temperature history of 48°C for 55 s is equivalent to a thermal dose of 43°C for 30 min. Once the temperature history at each node is determined, (i.e. $f(t)$), the thermal dose can be calculated at each node using formula [6]. To avoid having excessively high temperatures in the tissue near the electrodes, HYFEM.FOR can simulate a cooling fluid being pumped through the hollow electrodes. This fluid will circulate through the electrodes and carry excess heat away, thus protecting the healthy tissue surrounding the tumor from receiving a dangerous thermal dose.

A postprocessor HYFEMP.C has been written in C to display the numerical results derived by HYFEM.FOR. It can process 3-D images of temperature distributions, electrical fields and thermal dose distributions. It can also display 2-D temperature histories on selected points.

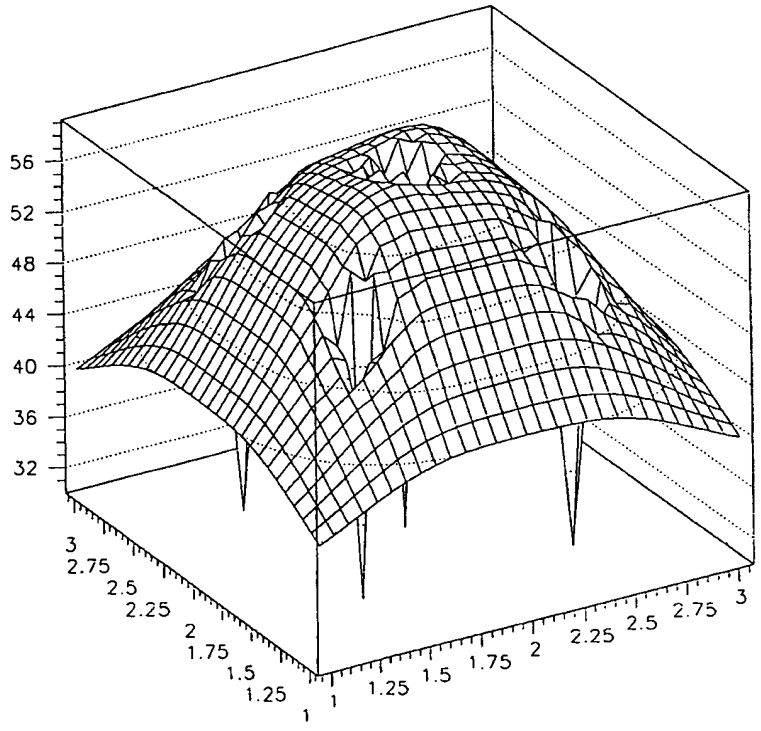

Fig. 5. 3-D temperature distribution.

3. Results

The numerical simulation has been conducted to simulate a 4 cm × 4 cm piece of tissue. Five electrodes are implanted inside of the tissue, as is shown in Fig. 1.

The radius of all the electrodes is 0.0165 cm and the electrical conductivity $\sigma = 0.0061/\Omega$. The thermal conductivity $k = 0.006$ W/cm °C, and $\rho c = 3$ W·s/cm^3 °C. Initial tissue temperature is 37°C and cooling fluid at 30°C is pumped in after heating for 40 s. In order to heat the tissue more uniformly, power in the electrodes is switched in a diagonal pattern. Two different power patterns of the electrodes are shown in Fig. 2a and 2b. Power in the electrodes is changed from the pattern in Fig. 2a to the one in Fig. 2b and changed back again every 5 min.

The electrical field is calculated first at each node. The 3-D voltage distribution at time 60 s and the power distribution contour are plotted by HYFEMP.C, as shown in Figs. 3 and 4, respectively.

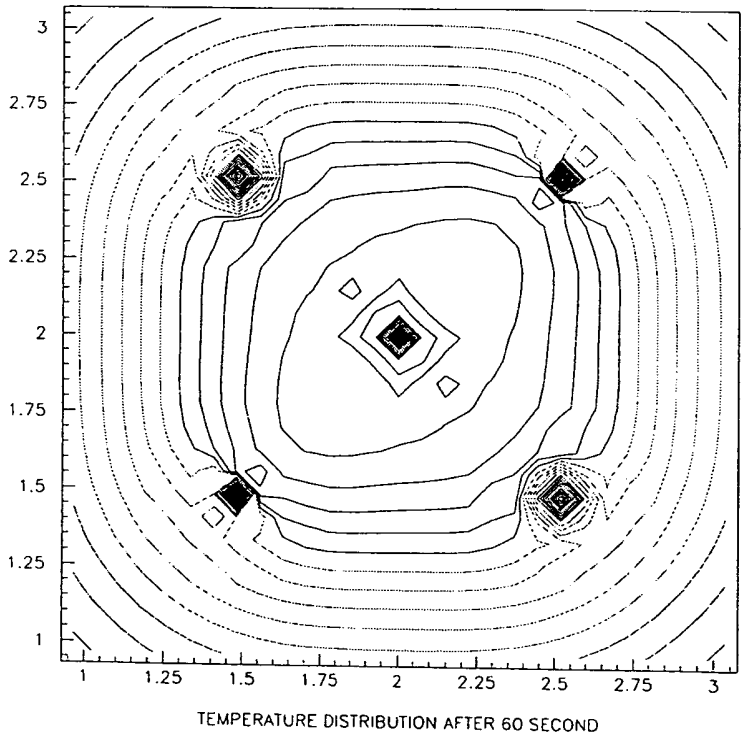

Fig. 6. Temperature distribution contour.

Consequently, the heating source Q_s in the bio-heat equation can be calculated by Eq. 5. Eq. 1 is then solved numerically to derive the temperature distribution. The 3-D image and contour of the temperature distribution at 60 s with cooling fluid through the electrodes are shown in Figs. 5 and 6 respectively.

Fig. 7 shows the temperature distribution without cooling fluid through the electrodes. Comparing Figs. 5 and 7, we observe that the temperature around electrodes will be so high as to damage normal tissue, unless cooling fluid is circulated through them. Fig. 8 shows the capabilities of such a system to heat a given volume of homogeneous tissue in 60 s to a thermal dose equivalent to 30 min or greater at 43°C. Five electrodes, indicated by dots in the figure, were placed in a symmetric pattern.

4. Conclusion

Typical regional heat treatments are aimed at producing hyperthermia of approx. 30–45 min at temperatures in excess of 42°C. According to our results, a thermal

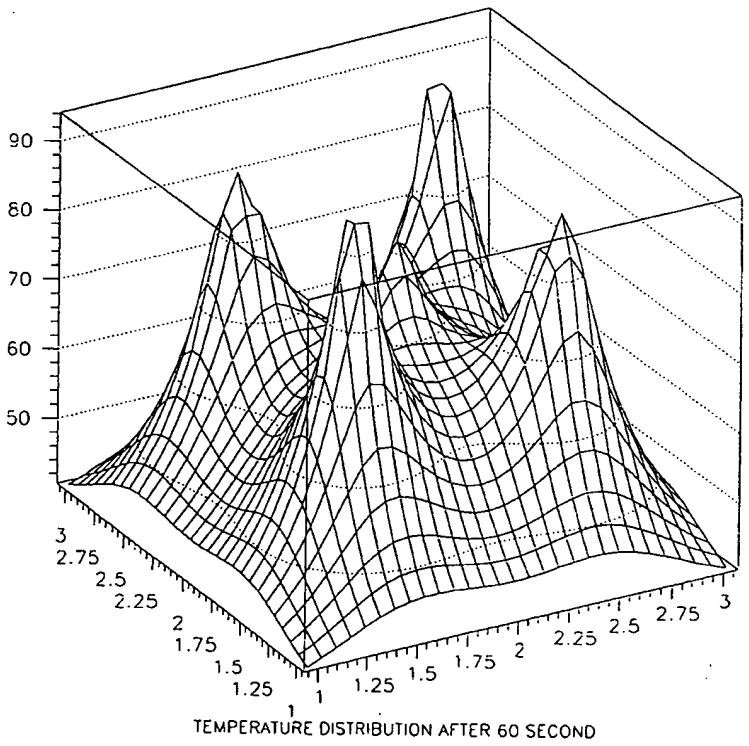

Fig. 7. 3-D temperature distribution without cooling fluid.

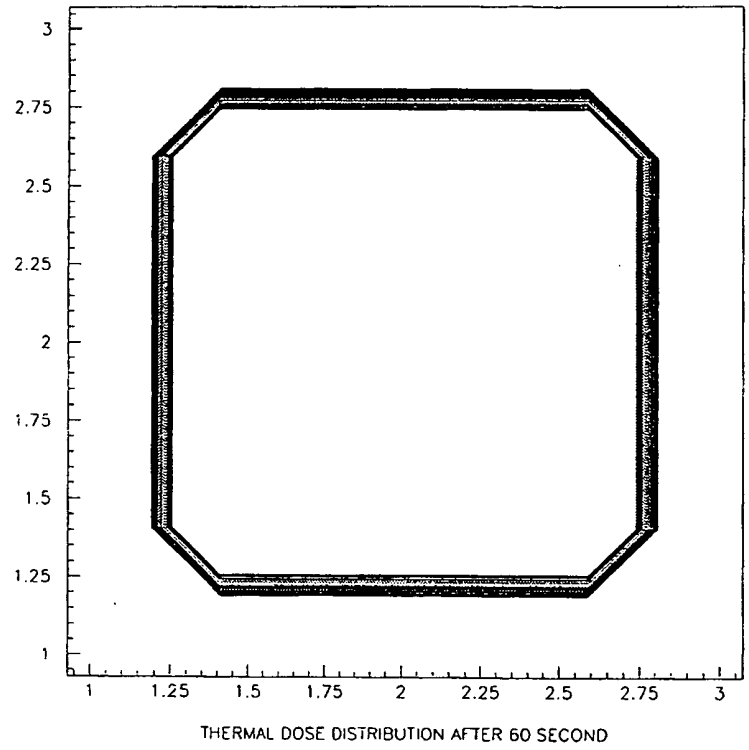

Fig. 8. Thermal dose plot for transient heating of tissue.

dose equivalent to or greater than 30 min at 43°C can be achieved within 60 s by rapidly heating the tissue with implanted rf electrodes. Therefore, the use of the high temperature of hyperthermia appears feasible for the treatment of cancer. There are several advantages to this rapid heating technique. First, it may be possible to stop blood flow to a tumor, or an extremity containing a tumor, for a period of one minute without harming healthy tissue. In such case, the variability in tumor temperature due to blood flow will be eliminated. After the treatment, blood flow can be restarted to save healthy tissue downstream from the tumor. We observed that the tissue temperature around the electrodes could become relatively high. Thus pumping cooling fluid through the electrodes is necessary to prevent the temperature from exceeding 58°C and causing serious tissue injury.

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